Physical Exercise for Secondary Osteoporosis

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Abstract: Bone loss caused by an underlying medical illness or associated treatment is often termed secondary osteoporosis and is a growing concern for a variety of patients. Exercise has demonstrated efficacy in maintaining bone health for individuals with age-related osteoporosis and its application to other clinical populations with specific interest in preserving bones is being increasingly explored. While there are many causes of secondary osteoporosis, only a few clinical populations have been studied for the role of exercise as a non-pharmacologic approach to bone preservation. This article briefly reviews secondary osteoporosis and the effect of exercise on bone health, while highlighting the current exercise intervention literature on bone outcomes for several clinical populations.

Keywords: Bone, exercise, physical activity, secondary osteoporosis.

INTRODUCTION

Given the multiple, significant functions of bone, its healthy development and maintenance are of great importance. Compromised bone health is a growing concern for researchers and clinicians due to the personal, social, and economic burden associated with the treatment of fractures and related comorbidities [1-3]. Unfortunately, many persons with chronic disease and those undergoing treatments for acute conditions may be susceptible to secondary osteoporosis. Exercise has demonstrated significant bone-related benefits in healthy children and adults [4-9], and may be the most readily modified lifestyle factor that can contribute to bone health and reduction in fracture risk in clinical populations [10-12]. This paper provides a scoping review of the current evidence for exercise on bone outcomes in patients with or at risk for secondary osteoporosis.

SECONDARY OSTEOPOROSIS

Secondary osteoporosis is bone loss and increased fracture risk due to underlying morbidity and/or associated treatment [13]. For many individuals, this bone loss is exacerbated by poor dietary intake of vitamin D or calcium, and/or reductions in physical activity and exercise due to disease or treatment-related fatigue or malaise [14-17]. The World Health Organization (WHO) classifies osteoporosis as a BMD < 2.5 standard deviations below the mean of healthy young women [18, 19] and has supplemented this criterion with the Fracture Risk Assessment Tool to further stratify fracture risk [20]. The annual costs associated with osteoporotic fractures are approximately $17.9 billion (USD) in the United States [2], however the specific costs associated with osteoporotic fractures that are secondary to underlying morbidity is unknown. Given the substantial physical, social, and economic costs associated with osteoporosis, researchers and clinicians are challenged to find ways to preserve and/or recover bone health.

Many disorders and treatments well-known to cause secondary osteoporosis, including: hypogonadism (idiopathic or induced chemically or surgically for cancer treatment) [21-26], glucocorticoid use [27-29], hyperthyroidism [30-32], Cushing’s disease [33, 34], and diabetes mellitus [35, 36] (See Table 1 for a summary of mechanisms leading to reduced BMD and fracture risk in selected populations). Beyond these, there is a growing list of etiologies for secondary osteoporosis, that have stimulated several reviews in this field [37-42]. For many medical conditions, secondary osteoporosis screening may not be included in standard care, possibly leading to later diagnoses (e.g. following a fracture) and delayed treatment [37, 39]. Medical management of secondary osteoporosis targets the primary diagnosis, and strives to prevent fractures with interventions designed to improve bone density [39]. Treatment strategies for osteoporosis secondary to endocrine diseases typically focus on recovering normal levels of hormones through surgery, radiation, or pharmacologic intervention [39]. Age-related sex hormone deficiency is often treated with hormone-replacement therapy, but this treatment approach must be weighed against the risk of sex-hormone-linked cancers, such as breast and prostate cancer [39]. Bisphosphonates are...
frequently prescribed for secondary osteoporosis [43] with common indications in patients receiving glucocorticoid therapy [29], androgen deprivation therapy (ADT) for prostate cancer [44, 45], and for breast cancer patients receiving aromatase inhibitors or experiencing chemotherapy-induced ovarian failure [46-48]. RANKL inhibitors (e.g. Denosumab) have generated increased interest for their bone preserving and enhancing characteristics, and have shown therapeutic benefit for cancer treatment-induced bone loss (CTIBL) [49-51]. In addition to pharmacologic approaches, recommendations for increased vitamin D and/or calcium intake are common, despite inconclusive evidence regarding their efficacy [52]. However, a recent Cochrane review of five randomized trials (aggregate sample of n=274) by Homik et al. found that lumbar and radial BMD was improved 2 years after initiating vitamin D and calcium supplementation in patients receiving glucocorticoid treatment [53]. Current general recommendations for daily consumption are 800-1200mg/day and 800 IU/day, for calcium and vitamin D, respectively [39].

Beyond dietary and drug treatments, exercise has been increasingly recommended for its bone-stimulating properties for the general population and individuals with primary or secondary osteoporosis. For healthy adults, the American College of Sports Medicine (ACSM) makes the following exercise recommendations for bone preservation [10]:

**Frequency:** Weight-bearing, aerobic activities 3-5 days per week; resistance training and high-impact/plyometric activities 2-3 days per week.

**Intensity:** Moderate to high bone-loading forces.

**Time:** 30-60 minutes per day of aerobic and/or resistance exercises.

For patients with primary osteopenia or osteoporosis, a systematic review of 28 randomized controlled trials (RCTs), observed a reduction in falls and fall-related fractures in exercising patients in interventions that ranged from 10 weeks to 30 months (median duration = 26 weeks) [54]. Improvements in BMD ranged from 0.5% to 10.2% (mean improvement of approximately 2.5%), however, the most consistent, and arguably most important, finding throughout the trials is that exercise preserves BMD in low-BMD patients relative to non-exercising participants and improves muscular strength, endurance, and balance. These findings cumulatively confer reductions in fall and fracture risk. These important findings demonstrate that while exercise may not always provide direct or sizeable benefit to BMD in people with primary osteopenia or osteoporosis, it can mitigate BMD decline and prevent falls and/or fractures. These findings also underscore exercise guidelines for patients with primary osteoporosis that emphasize weight-bearing and resistance exercises in addition to balance training and avoidance of extreme flexion/extension/twisting that may cause fractures [55].

Amongst the guidelines for exercise training in various clinical populations, few discuss exercise considerations for secondary osteoporosis and fracture risk (See Table 2 for general clinical exercise recommendations and proposed considerations for secondary osteoporosis). While bonespecific exercise guidelines may not be necessary for every clinical group, a deeper understanding of the interaction between primary morbidity, secondary osteoporosis, and exercise is warranted as clinicians explore novel and holistic methods of BMD preservation and fall/fracture prevention. In the sections that follow, we briefly review the current literature on exercise interventions for the common causes of secondary osteoporosis.

**EXERCISE AND CANCER-RELATED BONE LOSS**

Cancer affects bone health through: a) direct effects of the cancer itself (osteosarcomas or metastatic lesions), b) toxic effects of cancer therapies that affect bone modeling processes, c) reductions of calcium and vitamin D absorption, or d) sedentary lifestyles related to cancer-related fatigue [16, 17, 56]. CTIBL is primarily associated with reduced circulating androgens and estrogens via induced hypogonadism in men and women associated with chemotherapy, hormonal therapy (including surgical castration) and irradiation [16, 17, 56, 57]. Chemotherapeutic agents, such as doxorubicin, methotrexate, and cyclophosphamide directly reduce bone mineral content (BMC) by increasing bone resorption and reducing bone formation [17, 57]. Radiation and other systemic drugs, such as glucocorticoids and cyclosporine, have also been correlated with bone loss in cancer patients [17, 57]. For gastric carcinoma patients, bowel and intestinal resection may also be associated with CTIBL resulting from calcium and vitamin D deficiency (due to limited dairy intake) as well as poor absorption of these nutrients [17, 57]. For hormone dependent cancers, such as cancers of the breast and prostate, controlling or completely diminishing sex hormones is a mainstay of treatment that results in significant CTIBL. Accordingly, these cancers have received a bulk of the attention in terms of research with exercise and bone outcomes.

**Exercise and Cancer-Related Bone Loss in Women with Breast Cancer**

Therapies for breast cancer, including surgery, chemotherapy, radiation therapy, and hormone therapy (i.e. anti-estrogens, aromatase inhibitors, and selective estrogen receptor modulators) are associated with several deleterious effects on body composition, such as increased total weight and fat mass as well as decreased lean mass and BMD, with negative survival and quality of life implications [17, 58-62]. Adjuvant hormone therapy for breast cancer is associated with premature menopause in as many as 40% of females less than 40 years and 50-100% of females greater than 40 years [63]. Early onset menopause, due to luteinizing hormone-releasing hormone agonists (LHRHa) and aromatase inhibitors, is related to significant bone degradation, via increased osteoclast activity [64-66]. Interestingly, tamoxifen, a frequently prescribed anti-estrogen, appears to preserve BMD in postmenopausal women and degrades BMD in premenopausal women, of which, the mechanisms are poorly understood [14, 17, 26, 67, 68].

A growing body of research describes numerous benefits for breast cancer patients who exercise during and after treatment [69, 70]. More than 70 controlled trials have examined exercise in breast cancer patients and survivors;
however, only seven have examined bone health outcomes [71-77]. Studies assessing bone health in breast cancer patients have typically included women who are peri- or postmenopausal [71-76, 78], are at least 6 months post primary chemotherapy or radiation therapy [71, 72, 75-77] and receiving adjuvant selective estrogen receptor modulators or aromatase inhibitors [71-77]. Three RCTs showed that exercise may prevent the typical loss of BMD experienced in patients that are not exercising [71, 77, 78]. Bisphosphonates appear to provide better treatment for CTIBL in breast cancer patients than exercise [74], however exercise plus bisphosphonates appears to be better than bisphosphonates alone [76].

In a pre- post-test design, Knobf and colleagues assessed the effects of a 16 to 24 week, weight-loaded aerobic exercise intervention for 26 Stage I and II pre- or peri-menopausal breast cancer patients who had completed chemotherapy and/or radiation therapy (27% of whom were also undergoing adjuvant hormonal therapy with tamoxifen or aromatase inhibitors) [72]. The supervised, community-based intervention consisted of treadmill walking while wearing a weight belt and weighted backpack, three times per week. After 12 weeks, the weighted backpack was removed from the intervention protocol due to the exacerbation of arm lymphedema in one patient. No significant changes from baseline to 12 or 24 weeks were observed for body composition (lean mass, fat mass, or weight) or serum biomarkers of bone remodeling (osteocalcin and N-terminal propeptides of type I collagen [NTX]). No changes were observed for lean muscle mass, body fat percentage, or BMD as assessed by dual energy x-ray absorptiometry (DEXA). As changes in serum markers of bone remodeling and BMD were absent, this study reconfirms the bone-maintaining properties of weight bearing aerobic exercise. Moreover, the finding of arm lymphedema exacerbation, which may be associated with wearing a weighted backpack, has important implications for cancer-exercise specialists, particularly those motivated to increase strain magnitude to aid bone maintenance and recovery.

A single blinded RCT by Winters-Stone and colleagues studied the effect of a 1-year moderate-intensity resistance plus impact-loading exercise intervention versus progressive stretching (control intervention) in 106 women who were 1 year post treatment for early stage breast cancer [77]. The impact loading exercises involved two-footed, 1 inch jumps, with weighted vests. The primary endpoints for this study were body composition parameters (BMD, lean mass, and fat mass) using DEXA. Additionally, the investigators assessed systemic markers of bone turnover (serum osteocalcin and urinary deoxypyridoline crosslinks). At the 12-month follow-up, participants in the exercise intervention maintained lumbar spine BMD compared to losses observed in control subjects (0.47% change vs. -2.13% change, p<0.01). There were no between-group differences in total body or hip BMD. Interestingly, osteocalcin, a marker of bone formation, improved more in the control group than in the exercise group (1.59% change vs. 26.5% change, p<0.01). They also found that the exercise significantly improved lean mass in women receiving adjuvant hormone therapy (aromatase inhibitors), compared to non-exercising participants who were not receiving hormone therapy. These results suggest that fracture risk in the lumbar spine can be reduced with resistance training and plyometric-type exercises, but hip and total body BMD may be unresponsive to this particular intervention. The authors suggest that loading in unique/novel planes (rather than vertical), as well as exercise at a higher intensity or longer durations, may be required for adequate bone remodeling to occur in the hip [77].

Schwartz and colleagues were the first to examine the effect of exercise on bone health outcomes specifically for breast cancer patients currently receiving chemotherapy [78]. In their three-arm RCT, 66 stage I-III breast cancer patients were assigned to usual care, resistance exercise or aerobic exercise for 6 months. Subjects in the aerobic exercise intervention were encouraged to perform aerobic exercise of their preference, such as walking or jogging, for 15 to 30 minutes, four times per week at a moderate intensity. Resistance training subjects were instructed to complete four upper and four lower body exercises using resistance bands for two sets of 8-10 repetitions, four times per week. Participants in the usual care control group were neither encouraged nor discouraged from exercising. Based on an intention-to-treat analysis, only aerobic training had a significantly higher (as measured by percent change) lumbar spine BMD compared to controls (mean difference = 7.1; 95% CI = -1.98 – 0.14; p=0.02). Similar differences between the aerobic exercise group and control subjects were observed in analyses that controlled for menopausal status. It is also important to note that, although all participants started the trial with healthy BMD levels (i.e. not osteopenic or osteoporotic), seventeen women were osteopenic or osteoporotic by the end of the trial. While the results of this trial suggest that weight bearing aerobic exercise may be more beneficial than resistance training when compared to usual care, the intensity of the resistance training (using resistance bands) likely lacked sufficient loading to induce physiologic changes to the bone. Accordingly, it may not compare well to weight bearing aerobic activities. More research that specifically assesses the effects on bone health and fractures is warranted given these promising findings. Interestingly, two studies failed to describe BMD outcomes despite assessing body composition with DEXA [79, 80]. This non-reporting of BMD outcomes is likely due to null findings which may be attributed to the fact that patients generally had healthy BMD levels at the onset of these trials. To critically address this issue, stratified analysis of patients with and without impaired BMD is required.

The examination of bone health in breast cancer patients is of growing interest, but remains scant in the collective body of exercise and breast cancer research. Interesting findings have been produced by Schwartz and Winters-Stone suggest the lumbar spine may be particularly amenable to weight-bearing exercise, while hip BMD may require different approaches to exercise training to facilitate BMD preservation or improvement. This emerging literature has, for the most part, utilized strong methodological design and DEXA to assess changes in BMD with exercise. Future studies are required to determine the effect of different exercise patterns with and without the use of bisphosphonates on breast cancer patients with osteoporosis.
Exercise and Cancer-Related Bone Loss in Men with Prostate Cancer

In men, circulating androgens and estrogen play fundamental roles in the maintenance of BMD [22, 68]. For many men with prostate cancer, hormonal therapy via LHRHa, orchiectomy and anti-androgens is a prevalent form of treatment. The induced hypogonadism by LHRHa and orchiectomy has significant negative effects on BMD, which have been widely examined [21, 24, 81-91]. ADT can cause BMD reductions of 6.6% and 10% over the first two years after LHRHa and orchiectomy, respectively; with further reductions of 2% per year thereafter [85]. Shahinian et al. examined the records of 50,613 prostate cancer patients from the Surveillance, Epidemiology, and End Results (SEER) database and found that men that survived for 5 years or more post-diagnosis had a fracture risk of 19.4% if they received androgen deprivation therapy (ADT) versus 12.6% for men that did not receive ADT [24]. Moreover, a history of skeletal fractures (of the hip, spine, or extremity) were negatively associated with survival in a prospective cohort study of 195 men receiving ADT [90].

Given the prevalence and severity of bone degradation in this population, several authors have suggested exercise as a possible lifestyle approach to mitigate this side effect (e.g. [21, 81, 85, 92]). Despite the recommendations for exercise, in a recent observational study, only 7 of 66 (11%) patients undergoing ADT reported discussing lifestyle changes, including exercise, with their physician [93], a finding that contradicts other reports that urologists and radiation oncologists report discussing such lifestyle interventions with ADT-treated patients a majority (~60-80%) of the time [94]. The profound effect of hormone therapy on bone health in prostate cancer patients suggests that more studies should examine exercise as a bone preservation intervention in this population. To date, only Galvao and colleagues have reported on bone outcomes for prostate cancer patients in their 20-week, intensive resistance exercise program [95]. In this pre- post-test design of ten androgen-deprived patients, participants were trained with 12 upper- and lower-body exercises at 6- 12-repetition maximum, including: chest press, seated row, shoulder press, latissimus pull-down, triceps extension, biceps curl, leg press, squat, leg extension, leg curl, abdominal crunch, and back extension (using machines). The results of the study showed significant improvements from baseline in muscle strength (upper and lower body measures; p<0.001), functional fitness measures (p<0.05), and quadriceps thickness (p<0.05). In this trial, BMC and BMD (measured by DEXA) were preserved over the 20-week study duration. Also notable was that the high intensity exercise did not affect prostate specific antigen (PSA), growth hormone, or free testosterone levels, which are markers of disease progression, suggesting that exercise is safe in men with induced hypogonadism in terms of prostate cancer progression. A follow-up study by this group is currently being conducted by the same group, with the primary endpoints of total body, hip, and vertebral BMD measured by DEXA in a multi-centre, RCT of 195 men receiving ADT for prostate cancer [96]. This is a potential landmark study, in that it may be the first to examine the effects of exercise in an RCT sufficiently powered to assess bone changes in non-osteoporotic men undergoing hormone therapy for prostate cancer.

Two additional studies evaluated exercise interventions with prostate cancer patients using DEXA for body composition, but did not report BMD or BMC as primary or secondary outcomes [97, 98]. Galvao and colleagues conducted a RCT examining the effects of a mixed-modality (resistance and aerobic exercise training) for 57 prostate cancer patients receiving ADT [97]. Although they noted significant improvements in lean mass for intervention subjects compared to controls measured by DEXA (p<0.05), BMD findings were not reported. However, they did report modest improvements in balance (measured by the 6 meter backward walk test) (p=0.039) and the Activities-Specific Balance Confidence Scale (p=0.061) which may have preventative effects on falls and fractures. Segal and colleagues compared aerobic exercise training and resistance exercise training over 24 weeks in prostate cancer patients undergoing radiation therapy, of whom more than 60% were also on adjuvant ADT [98]. Resistance training proved more effective than aerobic exercise training when compared to controls, in terms of aerobic and musculoskeletal fitness, quality of life, and body fat percentage measured by DEXA (p<0.05). Again, bone outcomes were not reported. Collectively, this young body of literature suggests that exercise can produce muscular benefits that may reduce falls and subsequent fractures. Moreover, early findings suggest that there is bone preservation in exercising ADT-treated prostate cancer patients, which will be thoroughly investigated in the current trial by Newton [96].

Exercise and Acute Lymphoblastic Leukemia

Children with acute lymphoblastic leukemia (ALL) often present with osteoporosis-range BMD scores related to their chemotherapy, which may persist into adulthood [99, 100]. To preserve BMD in childhood ALL survivors, Hartman et al., examined the effects of a 2-year exercise program on total body and lumbar spine BMD as well as motor performance and ankle flexibility in 67 children and adolescents with ALL (median age of 5.4 years) [101]. In this RCT, exercising subjects completed hand, leg, and ankle function exercises, as well as short-burst, high-intensity activities (such as jumping) in a home-based format with follow-ups every 6 weeks. Endpoints were measured at baseline (time of diagnosis), 8 and 12 months after diagnosis, discontinuation of treatment (2 years after diagnosis), and 1 year after discontinuation of treatment (3 years after diagnosis). Only 48% of the study group exercised more than once per week. The results of the trial indicated no between-groups differences for BMD or motor performance at any of the follow-ups. The authors surmised that the lack of effect on bone and performance outcomes was likely due to poor adherence in the exercise group, a noted challenge in many cancer-exercise trials. Furthermore, the challenge of engaging a very young (median age = 5.8 years, age range = 1.7-17.1 years) population in routine, controlled exercises, likely rests with determination and attention of their parents, further complicating this approach.

This area deserves further investigation since children treated for ALL are likely to experience lifelong BMD related fractures (of the hip, spine, or extremity) were negatively associated with survival in a prospective cohort study of 195 men receiving ADT [90]. Given the prevalence and severity of bone degradation in this population, several authors have suggested exercise as a possible lifestyle approach to mitigate this side effect (e.g. [21, 81, 85, 92]). Despite the recommendations for exercise, in a recent observational study, only 7 of 66 (11%) patients undergoing ADT reported discussing lifestyle changes, including exercise, with their physician [93], a finding that contradicts other reports that urologists and radiation oncologists report discussing such lifestyle interventions with ADT-treated patients a majority (~60-80%) of the time [94]. The profound effect of hormone therapy on bone health in prostate cancer patients suggests that more studies should examine exercise as a bone preservation intervention in this population. To date, only Galvao and colleagues have reported on bone outcomes for prostate cancer patients in their 20-week, intensive resistance exercise program [95]. In this pre-post-test design of ten androgen-deprived patients, participants were trained with 12 upper- and lower-body exercises at 6-12-repetition maximum, including: chest press, seated row, shoulder press, latissimus pull-down, triceps extension, biceps curl, leg press, squat, leg extension, leg curl, abdominal crunch, and back extension (using machines). The results of the study showed significant improvements from baseline in muscle strength (upper and lower body measures; p<0.001), functional fitness measures (p<0.05), and quadriceps thickness (p<0.05). In this trial, BMC and BMD (measured by DEXA) were preserved over the 20-week study duration. Also notable was that the high intensity exercise did not affect prostate specific antigen (PSA), growth hormone, or free testosterone levels, which are markers of disease progression, suggesting that exercise is safe in men with induced hypogonadism in terms of prostate cancer progression. A follow-up study by this group is currently being conducted by the same group, with the primary endpoints of total body, hip, and vertebral BMD measured by DEXA in a multi-centre, RCT of 195 men receiving ADT for prostate cancer [96]. This is a potential landmark study, in that it may be the first to examine the effects of exercise in an RCT sufficiently powered to assess bone changes in non-osteoporotic men undergoing hormone therapy for prostate cancer.

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This area deserves further investigation since children treated for ALL are likely to experience lifelong BMD
challenges with heightened risk for fractures. The dearth of literature in this area is complicated by the young age of the cohort combined with the common exercise adherence problems of cancer exercise trials. Thus, creating age-appropriate exercise interventions that are conducive to adherence during cancer treatment are necessary to properly measure the impact of exercise on BMD in children. Subsequently, examination of exercise in adults with a history of childhood ALL is warranted to assess whether physical activity can beneficially augment fracture risk in this population.

EXERCISE AND BONE HEALTH FOR HEART TRANSPLANT RECIPIENTS

For patients undergoing heart transplantation, immunosuppression with glucocorticoids is a standard of care to facilitate host acceptance of the allograft and is associated with significant bone loss [102, 103]. Moreover, studies have demonstrated that 44% of all heart transplant recipients (HTR) have long bone fractures within the early post-operative period, and 35% of HTRs have non-traumatic, compression fractures of the lumbar vertebrae likely due to compromised bone integrity [102, 104]. Glucocorticoids affect vitamin D metabolism and decrease calcium absorption while increasing calcium excretion, causing a net loss in calcium and stimulating parathyroid hormone, an agonist of bone resorption [104, 105].

Accordingly, researchers have sought to identify mechanisms by which the compromised bone health and fracture risk in HTRs can be mitigated [106, 107]. Braith and colleagues randomly assigned 16 HTRs to either a 6-month resistance exercise program or a usual care, control group. Total body, femoral neck, and lumbar spine BMD was assessed by DEXA at baseline, 2 months following transplantation (at the beginning of the exercise intervention), and 3 and 6 months after the initiation of the exercise intervention. The exercise intervention consisted of supervised resistance exercise training, two days per week for 6 months, progressing from 50% of 1 repetition maximum (RM; the maximum amount of weight one can lift in one repetition) by 5% and 10% increments when the patient could complete 15 repetitions comfortably. The prescribed exercises included lumbar extension, decline chest press, knee extension and flexion, pullovers, triceps extension, biceps flexion, shoulder press, and abdominal exercises. Results from the trial showed that both groups had significant declines in BMD from pre-transplantation to 2 months following transplantation (p<0.05). The treatment group restored 99% of their total body BMD after 6 months of resistance training, while the control group had 7% less total BMD (p<0.05 in between-group analysis versus control group at 6 months follow-up). Similarly, the femoral neck and lumbar BMD as well as measures of total BMC and calcium were returned to near baseline values for the treatment group versus a continuous decline in BMD at 3 and 6 months for the control group.

Braith and colleagues expanded on their initial study with HTRs to assess whether there was added benefit of resistance exercise training to bisphosphonates in a 3-arm RCT [106]. In this study, 25 HTRs were randomly assigned to receive bisphosphonate treatment (alendronate, 10mg/day), resistance exercise training plus bisphosphonate, or no treatment for 6 months. The exercise plus bisphosphonate group received the same exercise program as in Braith’s original trial [107]. Participants in all three groups had significant reductions in total body, femoral neck, and lumbar spine BMD within 2 months of receiving the heart transplant prior to the intervention. At 3 and 6 months following the start of the intervention, the control group had continued to lose significant amounts of BMD, the bisphosphonate-only group had no further losses in BMD after initiation of treatment, whereas the bisphosphonate plus exercise group recovered almost all of their BMD to pre-transplantation levels.

The results of Dr. Braith’s and his colleagues’ work demonstrates the significant importance of an intensive, supervised resistance training program on BMD for HTR patients, which should be considered in standard cardiac rehabilitation. Unfortunately, little is known about the effect of common cardiac rehabilitation modalities (typically consisting of light-moderate intensity aerobic exercise) on bone health. Future studies in the field of cardiac rehabilitation, especially for HTRs, should consider using validated measures of BMD to assess potential changes in bone health.

EXERCISE AND BONE HEALTH IN PATIENTS WITH ARTHRITIS

While the etiology of rheumatoid arthritis and osteoarthritis are markedly different, the functional limitations, pain, and risk of osteoporotic fractures are similar and are discussed together [108-112]. Several studies have examined the effect of exercise on bone health for patients with rheumatoid arthritis that have provided conflicting findings [113-116]. Three, relatively small studies (n= 53-70) found little to no effect of aerobic or resistance training on bone outcomes for rheumatoid arthritis patients [113-115]. However, the general finding in these studies was that bone may be preserved, rather than improved, in exercising subjects compared to non-exercising controls but statistical significance was not achieved, likely due to sample sizes. In the largest exercise trial in this population to date, and one specifically powered to detect chronic bone changes, de Jong et al. randomized 309 rheumatoid arthritis patients to a high-intensity, mixed-modality training program or a non-exercise, usual care control group [116]. Exercising subjects participated in twice-weekly, supervised group-exercise for 75 minutes per session, that included 20 minutes of stationary cycling, circuit training (8-10 exercises), and sport or game activities. Over the two year follow-up period, participants in the exercise group had less total hip bone decay than did control participants (mean between groups difference; mixed-effects ANOVA p=0.026), but there was no difference in BMD at the lumbar spine.

For women with postmenopausal osteoarthritis, Song et al. (2010) recently examined the effects of a 6-month T’ai Chi program on muscle strength, BMD, and fear of falling. T’ai Chi represents an ideal modality for stimulating muscular strength and balance with implications for reducing falls [117]. In their RCT, intervention subjects received an arthritis-specific T’ai Chi program consisting of 31 forms of Sun-style T’ai Chi led by certified instructors for approxi-
The effect of exercise on bone health during weight loss remains equivocal and requires further study. However, it appears that when compared to diet-induced weight loss, comparable exercise-induced weight loss results in less bone deterioration; but when diet and exercise are combined, bone loss is similar to that of diet alone and reductions in BMD are proportionate to reductions in weight [128-130, 137]. Recent research by Silverman et al. suggest that exercise may result in improvements in BMD during weight loss, but these results require confirmation from a RCT. Given the negative relationship between health and obesity, weight loss programs will likely remain a popular research field, but must consider the detrimental effects on bone health when designing interventions.
EXERCISE AND BONE HEALTH IN STROKE PATIENTS

Chronic stroke patients are particularly vulnerable to fragility fractures due to prolonged inactivity, muscle weakness and loss of balance [138-141]. BMD is significantly reduced in the paretic limb [142, 143] and two studies have estimated that approximately 5% of stroke survivors experience a hip fracture within the first 3 years following a stroke [138, 139]. To counteract the bone loss, Pang et al. conducted a RCT in 63 chronic stroke patients assessing the effects of a 19-week intensive exercise intervention on BMD [144]. The community-based exercise program was designed to improve lower extremity bone strength, aerobic fitness, and balance using weight bearing, functional activities, such as brisk walking, sit to stand exercises, and step ups. As assessed by peripheral quantitative computed tomography, the experimental group showed a 5% increase in distal tibial trabecular BMC in the paretic limb compared to the control group, which had a 0.5% loss in BMC (p=0.048). No differences were found in the non-paretic limb. The effect of exercise on outcomes in this trial may have been blunted by exercise contamination in the non-intervention group, as they reported significant increases in physical activity over the course of the intervention. Given the limited amount of available evidence in this population, further studies are needed to confirm BMD and exercise relationships for stroke patients.

DISCUSSION

By 2025, the projected annual economic burden of osteoporotic-fractures is estimated to be more than $25 billion (USD) [3]. With an aging population more susceptible to chronic medical illnesses, secondary osteoporosis is likely to become a greater contributor to fractures and fracture related costs. Thus, lifestyle approaches like exercise are becoming a more prevalent adjunct management strategy for patients with secondary osteoporosis. However, the overall dearth of literature in this field is surprising given the stated physical, social, and economic burden associated with fractures in clinical populations. Early findings in breast and prostate cancer, arthritis, stroke, heart transplantation, and weight loss studies require additional research to confirm early findings and to examine physiologic mechanisms of bone preservation given various possible disease and drug interactions with exercise and bone. Moreover, preliminary research with multiple sclerosis patients who are also susceptible to secondary osteoporosis, have preliminary research to suggest that exercise may improve fracture risk through physical fitness and physical activity [145]. However, intervention studies in these populations using bone outcomes are not available. Given the prevalence of secondary osteoporosis in numerous clinical populations, it is likely that exercise related research specifically for bone outcomes will expand considerably.

Preliminary evidence from trials reviewed in this paper indicates that exercise is safe and likely confers a modest attenuating effect on bone loss for those that have or are at risk for secondary osteoporosis. Whether or not exercise provides clinically important differences to bone health in clinical populations requires further study but some trials suggest that falls and fall-related fractures may be reduced in patients with age-related osteoporosis [54]. The most clinically relevant trials related to bone health, will likely be long-term, adequately-powered RCTs that examine the role of exercise and the incidence of falls and fractures. To date, most studies have been underpowered to assess bone outcomes, have had limited follow-up durations (median = 6 months, maximum = 24 months), utilized mild forms of exercise training, and have not thoroughly examined or reported on adherence and potential contamination (between intervention and control groups). However, this early body of literature generally does consist of RCT designs and acute/sub-acute follow-up periods that have shown promising effects of exercise on musculoskeletal characteristics that may confer a fracture risk reduction.

The most promising line of research is the continued examination of combined exercise and pharmacologic approaches to bone health as early studies in this field suggest a possible synergistic relationship [76, 106]. RANKL inhibitors and bisphosphonates have demonstrated significant benefit for patients in terms of BMD and fracture risk, however, drug side effects and treatment costs may be prohibitive for some patients. As such, a lifestyle intervention including calcium and vitamin D combined with exercise may be an optimal complimentary strategy for maintaining bone health. Two studies investigated the combined effects of exercise plus pharmacologic treatment for BMD versus pharmacologic treatment alone [76, 106]. While exercise provided added benefits to bisphosphonates in both trials, neither study used a control group or an exercise-only group. A 2 x 2 factorial design RCT (exercise-only versus exercise plus drug versus drug-only versus control), is labor-intensive and costly, but would provide the most detailed understanding of exercise and drug intervention approaches for clinical populations with compromised bone health.

Exercise interventions for secondary osteoporosis have largely consisted of mild forms of training (weight bearing, aerobic exercises, standard resistance training regimens, etc.). Future research should address the effectiveness of high-intensity weight bearing activities, plyometrics, and resistance exercise training protocols that have been shown to be the most effective training characteristics for bone development in healthy populations[8, 146-148] and can be safely conducted in participants that are in their late nineties [149]. While traditionally not employed in clinical populations, several studies highlighted in this paper show that high-intensity resistance training appears to be feasible and safe. Galvao et al. (2006) demonstrated the safety of a progressively intense resistance training protocol in prostate cancer patients with a mean age was 70 years and actively undergoing hormone ablation [95]. Newton and colleague’s current trial, also with older, prostate cancer patients, employs a progressively intense plyometric-type intervention, including skipping, hurdle jumping, drop jumping, one-legged hopping, and leaping [96]. These studies will provide clarity to the types and intensity of exercise interventions that are safe, tolerable, and effective for maintaining and/or improving bone properties in what were previously considered frail or fragile populations.

Given the clinical significance of fractures, more long-term exercise trials that assess falls within clinical populations are required. The value of exercise in reducing falls and
Table 1. Summary of the Proposed Mechanisms Leading to Reduced BMD or Fracture Risk

<table>
<thead>
<tr>
<th>Cause of Secondary Osteoporosis</th>
<th>Mechanisms of Decreased BMD and Increased Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Osteosarcomas, metastatic lesions</td>
</tr>
<tr>
<td></td>
<td>Cancer-related fatigue → ↓ mobility, → ↓ PA</td>
</tr>
<tr>
<td>Cancer Treatment: Chemotherapy (e.g. doxorubicin, methotrexate, cyclophosphamide)</td>
<td>↑ bone resorption, ↓ bone formation</td>
</tr>
<tr>
<td></td>
<td>↓ vitamin D metabolism, ↓ calcium absorption</td>
</tr>
<tr>
<td>Cancer Treatment: Radiation</td>
<td>↑ calcium excretion → ↓ calcium absorption, ↑ parathyroid hormone</td>
</tr>
<tr>
<td></td>
<td>↓ vitamin D absorption, ↓ calcium absorption</td>
</tr>
<tr>
<td></td>
<td>↑ osteoclast activation due to damage to bone marrow cells causing ↑ inflammatory response</td>
</tr>
<tr>
<td>Cancer Treatment: Hormonal Therapy - Males</td>
<td>Hypogonadism → ↓ bioavailable testosterone → ↑ R:F</td>
</tr>
<tr>
<td></td>
<td>↓ lean mass → ↑ fall risk</td>
</tr>
<tr>
<td>Cancer Treatment: Hormonal Therapy – Females</td>
<td>Hypogonadism → ↓ bioavailable estrogen → ↑ R:F</td>
</tr>
<tr>
<td></td>
<td>Premature menopause (LHRHa, aromatase inhibitors) →↑ R:F</td>
</tr>
<tr>
<td>Glucocorticoid use (for cancer, heart transplantation, etc.)</td>
<td>↓ vitamin D metabolism, ↓ calcium absorption</td>
</tr>
<tr>
<td></td>
<td>↑ R:F → ↓ BMD</td>
</tr>
<tr>
<td></td>
<td>↑ muscular atrophy, ↓ metabolic rate, ↑ metabolic disorders → ↑ Adiposity → ↓ PA</td>
</tr>
<tr>
<td>Arthritis</td>
<td>↓ Mobility, ↑ Pain ↓ Joint function → ↓ PA</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoid use for RA (see above)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>↓ caloric intake (↓ calcium, ↓ vitamin D)</td>
</tr>
<tr>
<td></td>
<td>↓ estradiol → ↑ R:F</td>
</tr>
<tr>
<td></td>
<td>↑ R:F (all mechanisms are poorly understood)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Prolonged inactivity/non-weight bearing → Muscle atrophy → ↓ PA</td>
</tr>
<tr>
<td></td>
<td>↓ vitamin D exposure and intake, ↑ bone resorption</td>
</tr>
<tr>
<td></td>
<td>↓ Balance → ↑ risk of falling</td>
</tr>
</tbody>
</table>

Definitions: → = leads to; ↓ = decrease; ↑ = increase; BMC = bone mineral content; BMD = bone mineral density; PA = physical activity; RA = rheumatoid arthritis; R:F = bone resorption to formation ratio

Table 2. Exercise Guidelines and Considerations for Patients with Secondary Osteoporosis

<table>
<thead>
<tr>
<th>Condition Associated with Secondary Osteoporosis</th>
<th>General Exercise Guidelines</th>
<th>Exercise Considerations for Bone Health Promotion with Respect to Underlying Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTIBL</td>
<td>Frequency: 4-7 days per week</td>
<td>• Information re: the type and duration of treatment(s) is necessary for fall and fracture risk assessment; consider surgical grafts and various musculoskeletal imbalances</td>
</tr>
<tr>
<td></td>
<td>Intensity: AET = 50-80% of MHR; RET=50-75% of 1RM; 2-3 sets of 8-12 repetitions</td>
<td>• Information regarding bone metastasis is necessary to avoid heavy torque or load in areas of metastatic disease</td>
</tr>
<tr>
<td></td>
<td>Time: 15-60 minutes per session</td>
<td>• Exercise is generally symptom limited; symptoms may be localized or systemic due to disease or treatment</td>
</tr>
<tr>
<td></td>
<td>Type: large muscle groups with consideration for localized disease and treatment-related functional limitations</td>
<td>• Weight bearing, functional exercises are recommended to maintain independence and facilitate bone health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Balance training and lower extremity strength training is recommended to prevent falls given reduced balance and peripheral neuropathies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient concern that post exercise-related discomfort is associated with disease progression (i.e. metastatic bone pain) should be monitored and referral to physician for bone examination may be warranted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe deconditioning can negatively affect balance and increase fall/fracture risk; accordingly, balance should be trained and ambulatory exercises should be monitored closely</td>
</tr>
</tbody>
</table>
exercises for bone health[150]. The value of these campaigns will be challenged in the face of an aging population with sedentary lifestyles that heighten the risk for chronic disease and secondary osteoporosis. Population-based health outcome research, such as the Canadian Health Measures Survey, should include bone health, falls, and fracture data with concomitant collection of physical activity patterns that will enable researchers to assess long-term trends in bone health, relative to public campaigns designed to improve awareness of bone health issues.

**CONCLUSION**

Secondary osteoporosis is of growing interest to clinicians and researchers. Exercise has shown benefit in healthy populations and persons with primary osteoporosis. Accordingly, there is a movement in clinical exercise physiology to assess the value of exercise to assist in bone-related disorders secondary to various underlying pathologies and associated treatments. While the research is far from conclusive in this field, preliminary findings are promising and warrant further investigation. Campaigns that educate and promote physical activity within populations with chronic disease are justified given the strong evidence describing physical health benefits beyond bone health and fall risk. However, given the high importance and cost associated with bone health and falls, educational and interventional campaigns should specifically target patients who are at high risk for fragility fractures related to their condition or treatment. The studies presented in this paper

<table>
<thead>
<tr>
<th>Condition Associated with Secondary Osteoporosis</th>
<th>General Exercise Guidelines</th>
<th>Exercise Considerations for Bone Health Promotion with Respect to Underlying Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Transplant Recipients</td>
<td>Frequency: 3-5 days per week; Intensity: AET: RPE = 10-15 / 20; RET=50-60% of 1RM; 1-2 sets of 10-15 repetitions; Time: 15-60 minutes per session; Type: large muscle groups with consideration for localized disease and treatment-related functional limitations.</td>
<td>- Review type and duration glucocorticoid use to assess risk of osteoporosis. - Severe systemic deconditioning is common and intervention intensity and duration may be highly limited in early stages of exercise program. - Subjective RPE should be used to monitor intensity rather than HR. - Peripheral vascular disease and calf cramping is common and may result in symptom limited ambulation; patients with this condition should exercise in environments suitable to frequent rest periods. - Severe deconditioning may negatively affect balance and increase fall/fracture risk; accordingly, balance should be trained and ambulatory exercises should be monitored closely.</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Frequency: 3-7 days per week; Intensity: AET: 60-80% of MHR; RET= limited by affected joint; use pain tolerance to determine resistance for 2-3 sets of 8-12 repetitions; Time: symptom-limited; Type: large muscle groups with consideration for localized pain and dysfunction; aquatic fitness may be preferred; low impact exercises are recommended.</td>
<td>- For arthritis affecting the hands, use resistance bands that can be wrapped around hands rather than weights that may be too heavy for the patient to hold; similarly, exercise machines may be preferable to free weights. - Gentle and partial weight bearing exercises (e.g. walking or pool-based exercise) should be promoted rather than high-impact exercises that may exacerbate the arthritic condition and pain, resulting in further inactivity. - Prolonged periods of sedentary behavior due to arthritic pain may result in significant deconditioning and loss of balance; slow progression of exercise program with balance training is recommended. - Exercise may be preferable in the afternoon for rheumatoid arthritis patients that experience morning stiffness. - Monitor symptoms of pain and swelling associated with exercise; revise exercise program accordingly.</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Frequency: 4-7 days per week; Intensity: AET: ≥ 50-70% MHR; RET=60-70% of 1RM; 2-4 sets of 10-15 repetitions; Time: 15-60 minutes per session; Type: large muscle groups that result in highest metabolic cost while accommodating co-morbidities associated with obesity/overweight (e.g. arthritis, early onset of fatigue).</td>
<td>- Low impact exercises may be preferred due to joint pain; consider pool-based exercises that are only partial weight bearing; high-impact exercises for the lower extremities should be avoided. - Equipment modification or alternative modality selection may be necessary for using some RET or AET machines. - Consider caloric restriction interventions that may limit bioavailable energy substrates and subsequently reduce exercise intensity or duration. - Balance training and injury prevention is paramount to ensure exercise-induced weight loss can continue; measures to prevent falls and overuse injuries are recommended.</td>
</tr>
<tr>
<td>Stroke</td>
<td>Frequency: 3-5 days per week; Intensity: AET: 40-70% MHR; RET=50-60% of 1RM; 2-3 sets of 8-12 repetitions; Time: 20-60 minutes per session; Type: large muscle groups with consideration for unilateral weakness; loss of balance may result in primarily seated exercises.</td>
<td>- Balance assessment and training may be required before progressing to ambulatory exercise (if possible). - Ambulatory exercises should be closely monitored to prevent falls and associated fractures; if ambulation is not safely possible, AET may be conducted using an arm ergometer or cycle ergometer. - If unilateral weakness or dysfunction is present, RET loading may be proportionate to the strength of the specific muscles; or assistance may be provided from the contralateral (functional) muscle group. - Consider additional cardiovascular or psycho-cognitive comorbidities that necessitate further exercise program revision, including exercise environment/venue.</td>
</tr>
</tbody>
</table>

AET = aerobic exercise training; CTIBL = cancer treatment-induced bone less; HR = heart rate; MHR = maximal heart rate; RET= resistance exercise training; RM = repetition maximum; RPE = rating of perceived exertion (scale of 6-20).
describe the nascent, yet promising state of literature within the field and offer future directions for related research. Clinical exercise guidelines referring to bone preservation in various clinical groups should be updated with specific reference to bone-related outcome research in those areas. Specific research that builds on this preliminary evidence of the added effect of exercise to pharmacologic interventions, and the effectiveness of population-wide campaigns in preventing osteoporosis and fractures remain areas of high importance.

CONFLICTS OF INTEREST

The Authors have no conflicts of interest.

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